METHOD OF MAKING CROSSLINKED POLYMER MATRICES IN TISSUE TREATMENT APPLICATIONS

CROSS REFERENCES

This Application is a continuation of U.S. application Ser. No. 09/302,852, filed Apr. 30, 1999 and now U.S. Pat. No. 6,166,130 which is a continuation of U.S. application Ser. No. 09/229,851, filed Jan. 13, 1999 which issued as U.S. Pat. No. 6,051,648 on Apr. 18, 2000, which is a continuation of U.S. application Ser. No. 08/769,806, which was filed Dec. 18, 1996 which issued as U.S. Pat. No. 5,874,500 on Feb. 23, 1999, which is a continuation-in-part of U.S. application Ser. No. 08/573,799, filed Dec. 18, 1995, now abandoned, each of which are incorporated herein by reference in full.

FIELD OF THE INVENTION

This invention relates generally to crosslinked polymer compositions comprising a first synthetic polymer containing multiple nucleophilic groups crosslinked using a second synthetic polymer containing multiple electrophilic groups, and to methods of using such compositions as bioadhesives, for tissue augmentation, in the prevention of surgical adhesions, and for coating surfaces of synthetic implants, as drug delivery matrices and for ophthalmic applications.

BACKGROUND OF THE INVENTION

U.S. Pat. No. 5,162,430, issued Nov. 10, 1992, to Rhee et al., and commonly owned by the assignee of the present invention, discloses collagen-synthetic polymer conjugates prepared by covalently binding collagen to synthetic hydrophilic polymers such as various derivatives of polyethylene glycol.

Commonly owned U.S. Pat. No. 5,324,775, issued Jun. 28, 1994, to Rhee et al., discloses various insert, naturally occurring, biocompatible polymers (such as polysaccharides) covalently bound to synthetic, non-immunogenic, hydrophilic polyethylene glycol polymers.

Commonly owned U.S. Pat. No. 5,328,955, issued Jul. 12, 1994, to Rhee et al., discloses various activated forms of polyethylene glycol and various linkages which can be used to produce collagen-synthetic polymer conjugates having a range of physical and chemical properties.

Commonly owned, copending U.S. application Ser. No. 08/403,358, filed Mar. 14, 1995, discloses a crosslinked biomalerial composition that is prepared using a hydrophobic crosslinking agent, or a mixture of hydrophilic and hydrophobic crosslinking agents. Preferred hydrophobic crosslinking agents include any hydrophobic polymer that contains, or can be chemically derivatized to contain, two or more succinimidyl groups.

Commonly owned, copending U.S. application Ser. No. 08/403,360, filed Mar. 14, 1995, discloses a composition useful in the prevention of surgical adhesions comprising a substrate material and an anti-adhesion binding agent, where the substrate material preferably comprises collagen and the binding agent preferably comprises at least one tissue-reactive functional group and at least one substrate-reactive functional group.

Commonly owned, U.S. application Ser. No. 08/476,825, filed Jun. 7, 1995, by Rhee et al., discloses bioadhesive compositions comprising collagen crosslinked using a multifunctionally activated synthetic hydrophilic polymer, as well as methods of using such compositions to effect adhesion between a first surface and a second surface, wherein at least one of the first and second surfaces is preferably a native tissue surface.

Japanese patent publication No. 07090241 discloses a composition used for temporary adhesion of a lens material to a support, to mount the material on a machining device, comprising a mixture of polyethylene glycol, having an average molecular weight in the range of 1000–5000, and poly-N-vinylpyrrolidone, having an average molecular weight in the range of 30,000–200,000.

West and Hubbell, *Biomaterials* (1995) 16:1.153–1156, disclose the prevention of post-operative adhesions using a photopolymerized polyethylene glycol-co-lactic acid diacrylate hydrogel and a physically crosslinked polyethylene glycol-co-polypropylene glycol hydrogel, Poloxamer 407®.

Each publication cited above and herein is incorporated herein by reference in its entirety to describe and disclose the subject matter for which it is cited.

We now disclose a detailed description of preferred embodiments of the present invention, including crosslinked polymer compositions comprising synthetic polymers which contain multiple nucleophilic groups crosslinked using synthetic polymers containing multiple electrophilic groups, and methods for using these compositions to effect adhesion between a first surface and a second surface (wherein at least one of the first and second surfaces is preferably a native tissue surface) or to effect the augmentation of tissue, or to prevent surgical adhesion, or to coat surfaces of synthetic implants, or for delivering drugs or other active agents, or for ophthalmic applications.

SUMMARY OF THE INVENTION

The present invention discloses a crosslinked polymer composition comprising a first synthetic polymer containing two or more nucleophilic groups, and a second synthetic polymer containing two or more electrophilic groups which are capable of covalently bonding to one another to form a three dimensional matrix.

A preferred composition of the invention comprises polyethylene glycol containing two or more primary amino groups as the first synthetic polymer, and polyethylene glycol containing two or more succinimidyl groups (a five-membered ring structure represented herein as $-N(COCH_2)_2$) as the second synthetic polymer.

In a general method for preparing a composition for the delivery of a negatively charged compound (such as a protein or drug), a first synthetic polymer containing two or more nucleophilic groups is reacted with a second synthetic polymer containing two or more electrophilic groups, wherein the first synthetic polymer is present in molar excess in comparison to tile second synthetic polymer, to form a positively charged matrix, which is then reacted with a negatively charged compound. In a general method for preparing a matrix for the delivery of a positively charged compound, a first synthetic polymer containing two or more nucleophilic groups is reacted with a second synthetic polymer containing two or more electrophilic groups, wherein the second synthetic polymer is present in molar excess in comparison to the first synthetic polymer, to form a negatively charged matrix, which is then reacted with a positively charged compound.

In a general method for effecting the nonsurgical attachment of a first surface to a second surface, a first synthetic polymer containing two or more nucleophilic groups is mixed with a second synthetic polymer containing two or more electrophilic groups to provide a reaction mixture; the reaction mixture is applied to a first surface before substan-